UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/716,393	11/17/2003	Quan Nguyen	70-000410US	4409

22798 7590 06/12/2007

QUINE INTELLECTUAL PROPERTY LAW GROUP, P.C.
P O BOX 458
ALAMEDA, CA 94501

EXAMINER	
BOWMAN, AMY HUDSON	
ART UNIT	**PAPER NUMBER**
1635	

MAIL DATE	DELIVERY MODE
06/12/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/716,393	NGUYEN ET AL.	
	Examiner	Art Unit	
	Amy H. Bowman	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 March 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *103-151 and 202-204* is/are pending in the application.

4a) Of the above claim(s) *104,114,115,124-126,130,135,143-151 and 202-204* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *103, 105-113, 116-123, 127-129, 131-134, and 136-142* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *17 November 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *12/10/04, 1/18/05, 2/17/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant's election with traverse of group I in the reply filed on 3/23/07 is acknowledged. The traversal is on the ground(s) that groups I and III should be examined together because can be searched together without creating a burden on the examiner. Applicant's assertion is based on the material difference between the groups as cited by the examiner. Applicant asserts that the fact that group III "can be practiced with a single stranded oligonucleotide, which does not involve the double stranded molecule of group I" is not applicable in the instant case because group III is closed to methods in which the RNA is double stranded.

Applicant is encouraged to review MPEP § 806.05(h) that explains restriction between product and process claims. As explained in the office action mailed on 2/20/07, the inventions can be shown to be distinct if either or both of the following can be shown: (1) the process for using the product as claimed can be practiced with another materially different product or (2) the product as claimed can be used in a materially different process of using that product. Therefore, the fact that the method of selectively attenuating expression of a target gene in a cell could be practiced with a single stranded oligonucleotide, which does not involve the double stranded molecule of group I is sufficient in establishing distinctness. The examiner acknowledges that the method as instantly recited is directed to double stranded molecules, but the method could be practiced with other types of molecules as well, thus meeting the criteria of MPEP § 806.05(h).

Applicant is reminded that where applicant elects claims directed to the product, and a product claim is subsequently found allowable, withdrawn process claims that depend from or otherwise include all the limitations of the allowable product claim will be rejoined in accordance with the provisions of MPEP § 821.04.

As pointed out by applicant, the examiner inadvertently omitted claim 114, which is intended to be included in group II.

The requirement is still deemed proper and is therefore made FINAL.

Claims 104, 114, 115, 124-126, 130, 135, 143-151, and 202-204, as well as subject matter that is not drawn to the elected invention/species is withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected inventions, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 3/23/07.

Priority

Applicant's claim for the benefit of a prior-filed application under 35 U.S.C. 119(e) or under 35 U.S.C. 120, 121, or 365(c) is acknowledged. Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 120 as follows:

The later-filed application must be an application for a patent for an invention which is also disclosed in the prior application (the parent or original nonprovisional application or provisional application). The disclosure of the invention in the parent application and in the later-filed application must be sufficient to comply with the

requirements of the first paragraph of 35 U.S.C. 112. See *Transco Products, Inc. v. Performance Contracting, Inc.*, 38 F.3d 551, 32 USPQ2d 1077 (Fed. Cir. 1994).

The disclosure of the prior-filed applications fail to provide adequate support or enablement in the manner provided by the first paragraph of 35 U.S.C. 112 for one or more claims of this application. The applications do not disclose each and every element of the instant claims. Therefore, the instant claims are accorded in effective filing date of the instant application, 11/17/03.

Should applicant disagree, applicant is encouraged to point to such support with particularity by line and page number.

Claim Objections

Claim 106 is objected to under 37 CFR 1.75 as being a substantial duplicate of claim 103. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k). Since claim 103 recites that the first caging group inhibits the RNA from initiating RNA interference, RNA interference would be prevented as recited in claim 106.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 121 rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 121 recites the limitation "the first binding moieties" in the claim. There is insufficient antecedent basis for this limitation in the claim. Recitation of "can bind at least one first bind moiety", for example, would obviate this rejection.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 103, 105-107, 112, 113, 116, 117, 120 and 121 are rejected under 35 U.S.C. 102(b) as being anticipated by Chaulk et al. (Nucleic Acids Research, 1998, Vol. 26, No. 13, pages 3173-3178).

The instant claims are directed to a composition comprising a caged RNA, the caged RNA comprising: an RNA comprising at least one double-stranded region, the double-stranded region comprising a sense strand and an antisense strand, the antisense strand comprising a region which is substantially complementary to a region of a target mRNA, and one or more first caging groups associated with the RNA, the first caging groups inhibiting the RNA from initiating RNA interference of the target

mRNA in a cell comprising the caged RNA. The claims are further directed to structural characteristics of the RNA, the caging groups, and labels.

Chaulk et al. teach a composition comprising a caged RNA, the caged RNA comprising a ribozyme, wherein the ribozyme has a double stranded region that comprises a sense and an antisense strand, wherein the antisense strand also has a region that is complementary to a region of a target mRNA and a caging group associated with the RNA that inhibits the RNA from interfering with the target RNA (see figure 1, for example). The caged RNA substrate was not cleaved. However, the uncaged RNA was site-specifically cleaved at a rate of 70-80% cleavage (see page 3176, second column).

The instant specification defines the term "RNA interference" to refer to "a phenomenon in which the presence of double-stranded RNA in a cell results in inhibition of expression of a gene comprising a sequence identical, or nearly identical, to that of the double-stranded RNA. The double-stranded RNA responsible for inducing RNAi is called an "interfering RNA." Expression of the gene is inhibited by the mechanism of RNAi as described below, in which the presence of the interfering RNA results in degradation of mRNA transcribed from the gene and thus in decreased levels of the mRNA and any encoded protein... In brief, double-stranded RNA introduced into a cell (e.g., into the cytoplasm) is processed, **for example** by an RNAse III-like enzyme called Dicer, into shorter double-stranded fragments called small interfering RNAs (siRNAs, also called short interfering RNAs)." Therefore, the specification does not close the term "RNA interference" to any specific mechanism. The ribozyme of Chaulk et al.

cleaves target RNA in a sequence specific manner and meets each of the limitations of the instant claim, thereby interfering with target RNA. Therefore, the ribozyme of Chaulk et al. would necessarily inhibit the RNA from initiating RNA interference, as instantly claimed.

As stated in the MPEP (see MPEP 2112), something that is old does not become patentable upon the discovery of a new property. Since the prior art ribozyme meets all of the structural limitations of the claims, the prior art ribozyme would then be considered to have the property of inhibiting RNA interference as claimed.

Chaulk et al. teach photo-chemical control of a ribozyme reaction by the site-specific modification of the 2'-hydroxyl nucleophile in the hammerhead system with a caging functionality, more specifically a 2'-nitro-benzyl group.

Therefore, the invention of the above claims is anticipated by Chaulk et al.

Claims 103, 105-108, 113, 116, 117, 120, 121, 131, 133, 134, and 136-138 are rejected under 35 U.S.C. 102(b) as being anticipated by Haselton, III et al. (US 6,017,758).

The instant claims are directed to a composition comprising a caged RNA, the caged RNA comprising: an RNA comprising at least one double-stranded region, the double-stranded region comprising a sense strand and an antisense strand, the antisense strand comprising a region which is substantially complementary to a region of a target mRNA, and one or more first caging groups associated with the RNA, the

first caging groups inhibiting the RNA from initiating RNA interference of the target mRNA in a cell comprising the caged RNA. The claims are further directed to structural characteristics of the RNA, the caging groups, and labels.

Haselton et al. teach photolabile caging groups covalently linked to an isolated nucleic acid molecule which reversibly prevents expression of the nucleic acid. Haselton et al. teach introducing the nucleic acid into a cell and exposing the cell to light, thereby unlinking the nucleic acid and the caging group and expressing the nucleic acid. Haselton teach that the nucleic acid can encode an antisense nucleic acid and when the caging group is unlinked, the active antisense nucleic acid can bind to and inactivate a complementary nucleic acid within the cell (see abstract). Haselton et al. teach that the nucleic acid that is linked to a caging group can be single or double-stranded and can be DNA or RNA (see column 3). Haselton et al. teach that delivery of the caged molecule to cells is enhanced by enhanced binding to a delivery vehicle such as a liposome (see column 4).

The instant specification defines the term "RNA interference" to refer to "a phenomenon in which the presence of double-stranded RNA in a cell results in inhibition of expression of a gene comprising a sequence identical, or nearly identical, to that of the double-stranded RNA. The double-stranded RNA responsible for inducing RNAi is called an "interfering RNA." Expression of the gene is inhibited by the mechanism of RNAi as described below, in which the presence of the interfering RNA results in degradation of mRNA transcribed from the gene and thus in decreased levels of the mRNA and any encoded protein... In brief, double-stranded RNA introduced into a cell

(e.g., into the cytoplasm) is processed, **for example** by an RNAse III-like enzyme called Dicer, into shorter double-stranded fragments called small interfering RNAs (siRNAs, also called short interfering RNAs)." Therefore, the specification does not close the term "RNA interference" to any specific mechanism. Since the nucleic acids of Haselton et al. are disclosed as being single or double stranded, the nucleic acids of Haselton et al. meet the structural limitations of the claims and would necessarily inhibit the nucleic acid from initiating RNA interference, as instantly claimed.

As stated in the MPEP (see MPEP 2112), something that is old does not become patentable upon the discovery of a new property. Since the prior art double stranded molecule meets all of the structural limitations of the claims, the prior art double stranded molecule would then be considered to have the property of inhibiting RNA interference as claimed.

Furthermore, instant claim 138 recites that the first caging group is a cellular delivery module. Since a liposome is a cellular delivery module, the liposome of Haselton et al. meets the instant limitation of a second caging group.

Therefore, the invention of the above claims is anticipated by Haselton et al.

Claims 103, 105-110, 112, 113, 116, and 121 are rejected under 35 U.S.C. 102(b) as being anticipated by McCaffrey et al. (Nature, Vol. 418, 2002, pages 38 and 39), as evidenced by Devroe et al. (BMC Biotechnology, 2002, 2:15, pages 1-5).

The instant claims are directed to a composition comprising a caged RNA, the caged RNA comprising: an RNA comprising at least one double-stranded region, the

double-stranded region comprising a sense strand and an antisense strand, the antisense strand comprising a region which is substantially complementary to a region of a target mRNA, and one or more first caging groups associated with the RNA, the first caging groups inhibiting the RNA from initiating RNA interference of the target mRNA in a cell comprising the caged RNA. The claims are further directed to structural characteristics of the RNA, the caging groups, and labels.

McCaffrey et al. teach that transgene expression can be suppressed in adult mice via RNAi by small-hairpin RNAs transcribed in vivo from DNA templates. These shRNAs are processed into functional siRNAs by cellular enzymes, as evidenced by Devroe et al. (see abstract). The resultant siRNAs are 21-nucleotide annealed duplexes.

The instant specification defines "caging group" as a moiety that can be employed to reversibly block, inhibit, or interfere with the activity (e.g., the biological activity) of a molecule (e.g., a polypeptide, a nucleic acid, a small molecule, a drug, etc.) and discloses that the caging groups can, e.g., physically trap an active molecule inside a framework formed by the caging groups. Typically, however, one or more caging groups are associated (covalently or noncovalently) with the molecule but do not necessarily surround the molecule in a physical cage. For example, a single caging group covalently attached to an amino acid side chain required for the catalytic activity of an enzyme can block the activity of the enzyme; the enzyme would thus be caged even though not physically surrounded by the caging group. Caging groups can be, e.g., relatively small moieties such as carboxyl nitrobenzyl, 2-nitrobenzyl, nitroindoline,

hydroxyphenacyl, DMNPE, or the like, or they can be, e.g., large bulky moieties such as a protein or a bead. Caging groups can be removed from a molecule, or their interference with the molecule's activity can be otherwise reversed or reduced, by exposure to an appropriate type of uncaging energy and/or exposure to an uncaging chemical, enzyme, or the like.

Due to the broad definition of the term "caging group" disclosed in the instant specification, the linker portion of the hairpin of McCaffrey et al. meets the instant limitation of a "caging group" because the presence of the linker portion inhibits the ability of the molecule to act as an active siRNA, whereas this caging group can be removed from the molecule by cellular enzymes, resulting in an active siRNA.

Therefore, the instant invention is anticipated by McCaffrey et al.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 103, 105-113, 116-121, 131, 133, 134, 136-138, and 141 are rejected under 35 U.S.C. 103(a) as being unpatentable over Chaulk et al. (Nucleic Acids Research, 1998, Vol. 26, No. 13, pages 3173-3178), in view of Haselton, III et al. (US 6,017,758), Elbashir et al. (The EMBO Journal, Vol. 20, No. 23, pages 6877-6888, 2001) and Hammond et al. (Nature, 2001, Vol. 2, pages 110-119).

The instant claims are directed to a composition comprising a caged RNA, the caged RNA comprising: an RNA comprising at least one double-stranded region, the double-stranded region comprising a sense strand and an antisense strand, the antisense strand comprising a region which is substantially complementary to a region of a target mRNA, and one or more first caging groups associated with the RNA, the first caging groups inhibiting the RNA from initiating RNA interference of the target mRNA in a cell comprising the caged RNA. The claims are further directed to structural characteristics of the RNA and the caging groups.

Chaulk et al. teach a composition comprising a caged RNA, the caged RNA comprising a ribozyme, wherein the ribozyme has a double stranded region that comprises a sense and an antisense strand, wherein the antisense strand also has a region that is complementary to a region of a target mRNA and a caging group associated with the RNA that inhibits the RNA from interfering with the target RNA (see figure 1, for example). The caged RNA substrate was not cleaved. However, the uncaged RNA was site-specifically cleaved at a rate of 70-80% cleavage (see page 3176, second column).

The instant specification defines the term "RNA interference" to refer to "a phenomenon in which the presence of double-stranded RNA in a cell results in inhibition of expression of a gene comprising a sequence identical, or nearly identical, to that of the double-stranded RNA. The double-stranded RNA responsible for inducing RNAi is called an "interfering RNA." Expression of the gene is inhibited by the mechanism of RNAi as described below, in which the presence of the interfering RNA results in

degradation of mRNA transcribed from the gene and thus in decreased levels of the mRNA and any encoded protein... In brief, double-stranded RNA introduced into a cell (e.g., into the cytoplasm) is processed, **for example** by an RNAse III-like enzyme called Dicer, into shorter double-stranded fragments called small interfering RNAs (siRNAs, also called short interfering RNAs)." Therefore, the specification does not close the term "RNA interference" to any specific mechanism. The ribozyme of Chaulk et al. cleaves target RNA in a sequence specific manner and meets each of the limitations of the instant claim, thereby interfering with target RNA.

Chaulk et al. teach photo-chemical control of a ribozyme reaction by the site-specific modification of the 2'-hydroxyl nucleophile in the hammerhead system with a caging functionality, more specifically a 2'-nitro-benzyl group. The instant specification does not define the term "label". Therefore, the 2'-nitro-benzyl caging group of Chaulk et al. meets the instant limitation of a label.

Chaulk et al. do not teach separate polyribonucleotides comprising a sense polyribonucleotide and an antisense polyribonucleotide 19 to 25 nucleotides in length, TT 3'overhangs, cellular delivery modules or kits.

It is noted that claims directed to a kit are considered obvious over the composition. USPTO personnel need not give patentable weight to printed matter absent a new and unobvious functional relationship between the printed matter and the composition (see MPEP 2106.01). It is considered obvious to formulate the product into a kit with instructions for assembling the RNA and the caging group for convenience

because it would save an experimenter time (e.g. measuring the reagents) and reduce waste.

Haselton et al. teach photolabile caging groups covalently linked to an isolated nucleic acid molecule which reversibly prevents expression of the nucleic acid. Haselton et al. teach introducing the nucleic acid into a cell and exposing the cell to light, thereby unlinking the nucleic acid and the caging group and expressing the nucleic acid. Haselton teach that the nucleic acid can encode an antisense nucleic acid and when the caging group is unlinked, the active antisense nucleic acid can bind to and inactivate a complementary nucleic acid within the cell (see abstract). Haselton et al. teach that the nucleic acid that is linked to a caging group can be single or double-stranded and can be DNA or RNA (see column 3). Haselton et al. teach that delivery of the caged molecule to cells is enhanced by enhanced binding to a delivery vehicle such as a liposome (see column 4).

Elbashir et al. teach chemically synthesized siRNA duplexes consisting of two separate RNA strands, wherein each strand is 21-23 nucleotides in length, preferably 21 nucleotides. The siRNA duplexes taught by Elbashir et al. comprise a sense and an antisense strand (see figure 1, for example). Elbashir et al. teaches duplexes with overhangs, as well as blunt ended duplexes. Elbashir et al. teach 2'-deoxythymidine and 2'-deoxy-guanosines (see figure 7).

Hammond et al. teach two methods for silencing specific genes, antisense and RNA interference. Hammond et al. teach that although antisense methods are straightforward techniques for probing gene function, the methods have suffered from

questionable specificity and incomplete efficacy (see page 110, column 1). Hammond et al. teach that dsRNAs have been shown to inhibit gene expression in a sequence-specific manner and that RNAi is a potent method, requiring only a few molecules of dsRNA per cell to silence expression.

It would have been obvious to one of ordinary skill in the art to utilize a photochemical caging group, as taught by Chaulk et al. or a photolabile caging group, as taught by Haselton et al. with a molecule having the structural characteristics of the siRNA of Elbashir et al. It would have been obvious to utilize a liposome to aid in the delivery of the molecule, as taught by Haselton.

One would have been motivated to utilize a photochemical or photolabile caging group, as used with the ribozyme and antisense nucleic acids of Chaulk et al. and Haselton et al., respectively to control the expression of the siRNA of Elbashir et al. because ribozymes, antisense nucleic acids, and siRNA molecules are each sequence specific inhibitors of target gene expression, each having the same delivery challenges within a cell. Furthermore, Hammond et al. teach that using dsRNA to inhibit gene expression is more sequence specific than using antisense methods and that RNAi is a more potent method, requiring only a few molecules of dsRNA per cell. Since antisense oligonucleotides, ribozymes and siRNAs were each known in the art to be used for the same purpose, inhibiting gene expression in a sequence specific manner, and it was known that dsRNA molecules were preferable inhibitory molecules, as evidenced by Hammond et al., one would have been motivated to utilize a siRNA instead of a ribozyme or antisense oligonucleotide to achieve the desired inhibition of the target

gene. Since photochemical or photolabile caging groups had already been successfully applied to ribozymes and antisense oligonucleotides, respectively, one would have been motivated to gain the same benefit of controlling the expression of a siRNA as well by covalently attaching the caging groups to a siRNA.

One would have been motivated to design the siRNA to be controlled by the caging group to be duplexes of 21 nt siRNAs with 2 nt 3' overhangs because Elbashir et al. teach that these siRNAs were the most efficient triggers of sequence-specific mRNA degradation via RNAi.

One would have been motivated to utilize a liposome to aid in the delivery of the siRNA of Elbashir et al. because Haselton et al. teach that delivery of caged molecules to cells is enhanced by enhanced binding to a delivery vehicle such as a liposome.

Finally, one would have a reasonable expectation of success to utilize a caging group with an siRNA with the structural characteristics of the siRNAs of Elbashir et al. given that caging groups had resulted in successful control of expression of ribozymes and antisense nucleic acids, as evidenced by Chaulk et al. and Haselton et al, respectively and the siRNAs of Elbashir et al. were taught to be the most efficient triggers of RNAi.

One would have a reasonable expectation of success that a liposome would enhance the delivery of the siRNA of Elbashir et al. because Haselton et al. teach enhanced delivery of an antisense nucleic acid with a liposome.

Thus in the absence of evidence to the contrary, the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention

was made.

Claims 103, 105-113, 116-121, 131-134, 136-138, and 141 are rejected under 35 U.S.C. 103(a) as being unpatentable over Chaulk et al. (Nucleic Acids Research, 1998, Vol. 26, No. 13, pages 3173-3178), in view of Haselton, III et al. (US 6,017,758), Elbashir et al. (The EMBO Journal, Vol. 20, No. 23, pages 6877-6888, 2001) and Hammond et al. (Nature, 2001, Vol. 2, pages 110-119), as explained in the 35 U.S.C. 103(a) rejection above, further in view of Schwartz et al. (Current Opinion in Molecular Therapeutics, 2000, 2(2), pages 162-167).

The instant claims are directed to a composition comprising a caged RNA, the caged RNA comprising: an RNA comprising at least one double-stranded region, the double-stranded region comprising a sense strand and an antisense strand, the antisense strand comprising a region which is substantially complementary to a region of a target mRNA, and one or more first caging groups associated with the RNA, the first caging groups inhibiting the RNA from initiating RNA interference of the target mRNA in a cell comprising the caged RNA. The claims are further directed to structural characteristics of the RNA and the caging groups.

Chaulk et al., Haselton, III et al., Elbashir et al., and Hammond et al. do not teach polypeptide cellular delivery modules.

Schwartz et al. teach that peptide and protein-mediated delivery systems are able to efficiently introduce DNA, antisense peptide nucleic acids, oligonucleotides,

small molecules and proteins into cells both in vitro and in vivo (see abstract, table 1, and page 163, for example).

It would have been obvious to one of ordinary skill in the art to utilize a peptide or protein-mediated delivery system, as taught by Schwartz et al. to aid in the delivery of the siRNA of Elbashir et al. with a caging group of Chaulk et al. or Haselton et al.

One would have been motivated to utilize a utilize a peptide or protein-mediated delivery system, as taught by Schwartz et al. because Schwartz et al. teach that such systems are able to efficiently introduce DNA, antisense peptide nucleic acids, oligonucleotides, small molecules and proteins into cells both in vitro and in vivo. Since Haselton et al. teach that delivery of the caged molecule to cells is enhanced by enhanced binding to a delivery vehicle such as a liposome, one would have been motivated to utilize a peptide or protein system that has delivery benefits as well, as taught by Schwartz et al.

Finally, one would have a reasonable expectation of success to utilize a peptide or protein delivery system as taught by Schwartz et al. because Haselton et al. teach that the delivery of caged nucleic acids had been enhanced via a liposome and therefore one would expect for the delivery of the siRNA of Elbashir et al. with a caging group to be further enhanced by a peptide or protein delivery system as well, given the delivery benefits taught by Schwartz et al.

Thus in the absence of evidence to the contrary, the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made.

Claims 103, 105-113, 116-123, 127-129, 131, 133, 134, and 136-142 are rejected under 35 U.S.C. 103(a) as being unpatentable over Chaulk et al. (Nucleic Acids Research, 1998, Vol. 26, No. 13, pages 3173-3178), in view of Haselton, III et al. (US 6,017,758), Elbashir et al. (The EMBO Journal, Vol. 20, No. 23, pages 6877-6888, 2001) and Hammond et al. (Nature, 2001, Vol. 2, pages 110-119), as explained in the first 35 U.S.C. 103(a) rejection above, further in view of Tyagi et al. (Nature Biotechnology, Vol. 14, 1996, pages 303-308).

The instant claims are directed to a composition comprising a caged RNA, the caged RNA comprising: an RNA comprising at least one double-stranded region, the double-stranded region comprising a sense strand and an antisense strand, the antisense strand comprising a region which is substantially complementary to a region of a target mRNA, and one or more first caging groups associated with the RNA, the first caging groups inhibiting the RNA from initiating RNA interference of the target mRNA in a cell comprising the caged RNA. The claims are further directed to structural characteristics of the RNA and the caging groups, as well as labels.

Chaulk et al., Haselton, III et al., Elbashir et al., and Hammond et al. do not teach fluorescent labels or configurations related to fluorescent labels.

Tyagi et al. teach nucleic acid probes that undergo a fluorogenic conformational change when they hybridize to their targets. Tyagi et al. teach that probes can find a complementary strand in the presence of a large excess of other nucleic acids by

labeling the oligonucleotide probes, immobilizing the hybrids on a solid surface matrix and then removing unhybridized probes.

Tyagi et al. teach single-stranded nucleic acid molecules that possess a stem-and-loop structure, wherein the loop portion of the molecule is a probe sequence that is complementary to a predetermined sequence in a target nucleic acid (see Figure 1). The stem is formed by annealing the two complementary arm sequences that are on either side of the probe sequence. A fluorescent moiety is attached to the end of one arm and a quenching moiety is attached to the end of the other arm. The stem keeps the two moieties in close proximity to each other, causing the fluorescence of the flourophore to be quenched by fluorescence resonance energy transfer. When the probe encounters a target molecule, it forms a hybrid that is longer and more stable than the hybrid formed by the arm sequences, causing a conformational change that forces the arms apart, resulting in fluorescence when illuminated by ultraviolet light.

It would have been obvious to one of ordinary skill in the art to utilize a fluorescent label that yields fluorescent emission in a donor-acceptor system, as taught by Tyagi et al. to detect the siRNA of Elbashir et al. with a caging group of Chaulk et al. or Haselton et al. It would have been obvious to immobilize the caged RNA to a matrix within an array.

One would have been motivated to utilize a label that emits a fluorescent signal when hybridized to a target nucleic acid, as taught by Tyagi et al. to detect the siRNA of Elbashir et al. with a caging group of Chaulk et al. or Haselton et al. because Tyagi et al. teach that such fluorescent label configurations offer real-time monitoring and

interactions that are extraordinarily specific. One would have been motivated to immobilize the caged RNA to a matrix within an array because Tyagi et al. teach that it is routine to use such a system to explore gene function.

Finally, one would have a reasonable expectation of success to utilize a label that emits a fluorescent signal when hybridized to a target nucleic acid, as taught by Tyagi et al. to detect the siRNA of Elbashir et al. with a caging group of Chaulk et al. or Haselton et al. because these fluorescent moieties were known to aid in the detection of nucleic acid molecules, as evidenced by Tyagi et al.

Thus in the absence of evidence to the contrary, the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and In *re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 103, 105-113, 116-123, 127-129, 131-134, and 136-142 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-4, 7-36, and 47 of copending Application No. 11/134,851 (US 2005/0282203 A1). Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims are directed to subject matter that overlaps in scope. The claims are each directed to caged RNAs and overlapping structural characteristics. The instant claims and the claims of application '851 are considered obvious over each other.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Amy H. Bowman whose telephone number is (571) 272-0755.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Doug Schultz can be reached on (571) 272-0763. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Amy H Bowman
Examiner
Art Unit 1635

AHB

/J. E. Angell/
Primary Examiner
Art Unit 1635